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A Smallpox and an Inhalation Anthrax Model Implemented Using Ordinary Differential Equations

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14 March 2006

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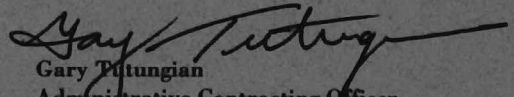

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ABSTRACT

This report presents one approach for modeling smallpox and inhalation anthrax outbreaks using ODEs (ordinary differential equations). This approach is related to a standard SEIR (susceptible exposed infected recovered) model. For each model, we define the states that characterize the uninfected and infected populations, the parameters governing disease progression, and the ODEs that govern the transitions between the population states. In both models, medical capacity and treatment limitations are considered. To quantify the benefit of an early public health response, the number of cases and deaths resulting from an outbreak are determined as a function of delay in public health response. The smallpox model indicates that early initiation of a mass vaccination campaign can significantly reduce the number of deaths. The anthrax model indicates that distribution of antibiotics at a high rate within the first day following a large attack can save nearly all those exposed. Future work will focus on replacing the ODEs with probability distribution functions based on data from outbreaks; doing so will lead to a more accurate model of the incubation periods and, in turn, a more accurate estimate of the benefit of an early response.

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1. INTRODUCTION

This report presents one approach for modeling smallpox and inhalation anthrax outbreaks using ODEs (ordinary differential equations). This approach is related to a standard SEIR (susceptible exposed infected recovered) model; see [2], for example. One benefit of such a simple framework is greater transparency and fewer model parameters that must be estimated and varied. Other types of models include more complicated ODE formulations [35] and stochastic formulations with homogeneous mixing [20] and heterogeneous mixing [6, 11]; homogeneous mixing assumes all people in the susceptible population are equally likely to become infected. See [8, 24] for a general review of these approaches.

The two ODE models are based on a framework of states described in section 2. For each model, we define subcategories of the primary states, the disease progression parameters, and the transition rates between the states. In both models, medical capacity and treatment limitations are considered. Smallpox is modeled as a single-stage illness with capacities defined for quarantine. Inhalation anthrax is modeled as a three-stage illness to which different medical treatments and capacities are applied.

2. DISEASE MODEL FRAMEWORK

The populations of both models can be separated into the six primary states shown in Table 1. For each model, these states are further broken down into additional states.

TABLE 1

Basic states of the disease models, which are functions of time

Disease States	Notation
Unexposed at time t	$U(t)$
Exposed people at time t	$E(t)$
Symptomatic people at time t	$S(t)$
Vaccinated people at time t	$V(t)$
Recovered people or people with immunity at time t	$R(t)$
Dead at time t	$D(t)$

Transitions between these states are governed by ODEs. Let $P(t) \in \mathcal{R}^n$ be a vector of the number of people in each state at time t, so that $P_k(t)$ is the number of people in the kth state of the model at time t. Given the initial conditions $P(t_0)$ and the differential equations, we can use Euler's method to estimate the number of people in each state at time t_n. Euler's method is a typical method for solving differential equations, using derivative information from the previous time step t_{n-1} to estimate the number of people in the kth state at time t_n:

$$P_k(t_n) = P_k(t_{n-1}) + P'_k(t_{n-1})\Delta t, \tag{1}$$

where $P'_k(t_{n-1})$ is the derivative of the kth population at time t_{n-1}. For convenience, we define

$$P'_k(t) = \sum_{i \in \mathcal{I}} f_{i,k}(t) - \sum_{j \in \mathcal{J}} f_{k,j}(t), \tag{2}$$

where $f_{i,k}(t)$ is the rate of people moving from the ith into the kth state at time t, $\mathcal{I}$ is the set of states that flow into the kth state, and $\mathcal{J}$ is the set of states into which the kth state flows ($\mathcal{I} \cap \mathcal{J} = \emptyset$). When the ith state does not flow into the jth state, $f_{i,j}(t) = 0$ for all t. For notational convenience when defining the rates $f_{i,j}(t)$, we replace the notation $f_{i,j}(t)$ with $f(i,j)$ and i and j with the notation for the states shown in Table 2.

Given the initial conditions, movement between the states will continue until everyone is either vaccinated, recovered (or immune) or dead. The initial conditions of the model are specified by the initial number of people infected, $E(t_0)$, and the initial number of people who are susceptible, $U(t_0)$. The total number of people in the simulation is

$$N_t = U(t_0) + E(t_0). \tag{3}$$

3. SMALLPOX MODEL

In the smallpox model, the six primary states, shown in Table 1, are subcategorized according to whether people are quarantined or isolated (q), unsuccessfully vaccinated (v), designated as having a traceable meeting with an infectious person (c), receiving treatment (t), or will die (d). In all, there are twenty-one states, as shown in Table 2.

TABLE 2

States of the smallpox model

Disease State	Notation: Categorized Disease States					
Unexposed	$U(t)$	$Uv(t)$	$Uq(t)$	$Uqv(t)$	$Uc(t)$	$Ucv(t)$
Exposed	$E(t)$	$Ev(t)$	$Eq(t)$	$Eqv(t)$	$Ec(t)$	$Ecv(t)$
Symptomatic	$S(t)$	$Sd(t)$	$Sq(t)$	$Sqd(t)$	$Sqt(t)$	$Sqtd(t)$
Vaccinated	$V(t)$					
Recovered	$R(t)$					
Dead	$D(t)$					

3.1 PARAMETERS OF THE SMALLPOX MODEL

The parameters of the model can be grouped into four categories: (1) disease progression, (2) prophylaxis effiacy, (3) public health response, and (4) resource limits. These parameters are presented in Tables 3–6.

Table 3 lists disease progression parameters for smallpox up to and including the infectious period. Smallpox has a relatively long incubation period followed by a non-infectious prodromal period, marked by high fever and flu-like symptoms, that is in turn followed by the infectious period, marked by the characteristic smallpox rash. Because the prodrome is assumed to be non-infectious, it is included in the incubation period. The final step to recovery is progression through a non-infectious scabbing period, which is not modeled. Thus, $R(t)$ is the number of individuals who have survived infection with immunity but who may not be fully physically recovered yet.

Currently, there is no treatment to improve the likelihood of survival once the rash has developed. However, we have included variables related to treatment (λ_t, ρ_t, and δ_t) in the model so that the model may be applied to an infectious disease that does have effective treatments or to model the outcome of a smallpox outbreak if an acceptable antiviral drug becomes available.

In the absence of any medical interventions, whether or not an outbreak becomes an epidemic depends on the value of the basic reproductive number, R_0; R_0 is defined as the expected average number of secondary infections resulting from a single infectious person in a fully susceptible pop-

TABLE 3

Smallpox disease progression parameters

Parameter	Notation	Value
incubation period (days)	α^{-1}	14.6 [10]
proportion of people expected to die	λ	0.30 [29]
infectious period given recovery (days)	ρ^{-1}	8.5 [10]
infectious period given death (days)	δ^{-1}	8.5 [10]
proportion of treated people expected to die	λ_t	0.30
infectious period given recovery with treatment (days)	ρ_t^{-1}	8.5
infectious period given death with treatment (days)	δ_t^{-1}	8.5
proportion of contacts infected	ϕ	0.20 [10]
average number of secondary infections	R_0	10 [27]
contacts per day per member of population	β	see equation (4)
general population ("herd") immunity	ϵ_h	0.20 in US [27]
environmental infections per day	γ	0

ulation. If $R_0 < 1$, then the outbreak will die out. However, if $R_0 > 1$ and no interventions are imposed to force $R_0 < 1$, then the disease will continue to spread. In this analysis, the contact rate between people, β, is defined as

$$\beta = \frac{R_0}{\phi N_t \left(\lambda \delta^{-1} + (1-\lambda)\rho^{-1}\right)}. \tag{4}$$

The definition of β ensures that at the outset of the outbreak each infectious person infects on average R_0 people. This is a standard way to define the contact rate; for a similar definition see [10] in which contact rate is defined as $\beta = R_0/(\phi N_t \delta_s^{-1})$ where δ_s^{-1} is the amount of time an individual is infectious [10].

TABLE 4

Smallpox prophylaxis efficacy

Parameter	Notation	Value
prophylaxis efficacy when uninfected	ϵ_u	0.975 [10]
prophylaxis efficacy when infected but latent	ϵ_e	0.30 [10]

Table 4 lists the assumed efficacy of the smallpox vaccine. The prophylaxis efficacy for those already infected is an approximation based on the fact that the vaccine should be effective at

preventing or reducing the severity of the illness if administered early during the incubation period, which may last between 9 to 14 days [25]. The window of opportunity for effective vaccination is estimated to be up to 4 days after infection [14].

TABLE 5

Smallpox public health response parameters

Parameter	Notation	Value
time elapsed before response is initiated (days)	κ	varied
individuals per 1 million given prophylaxis per day	ν	100,000 [28]
fraction of contacts traced	θ_c	varied
quarantine period (days)	σ^{-1}	16.7 [10]
average time delay to self-isolate or seek treatment	θ_s	0.95 [10]

TABLE 6

Resource limits for a smallpox outbreak

Parameter	Notation
daily prophylaxis available	M_v
total prophylaxis available	M_{vtotal}
daily new contact quarantine capacity	M_q
daily total contact quarantine capacity	M_{qtotal}
daily treatment capacity	M_t

Recently, there has been much debate about the proper response to a smallpox outbreak. See [6, 11, 18, 20, 35] for examples of mathematical models currently being used to compare control policies for a smallpox outbreak. In this paper, we consider three basic responses: (1) contact tracing and ring vaccination, the final strategy used during the smallpox global eradication campaign [7, 21]; (2) mass vaccination, like that used during the last mass vaccination campaign in the US [34] (which also included contact tracing [33]); and (3) these two responses in combination. In addition, the model can also simulate isolation of infectious people, which would also be another method of controlling an outbreak.

In the event of a smallpox outbreak, the current plan based on CDC guidelines is to use an "enhanced version of the surveillance-containment strategy that was successfully employed by the World Health Organization (WHO) to eradicate smallpox worldwide in the sixties and seventies" [28] and to resort to mass vaccination only if the surveillance-containment strategy does not appear

to be effective. In the case of mass vaccination, the plan is to vaccinate 100,000 people/day per million people in the area [28]. As of July 2003, the Massachusetts Emergency Management Association plan is to vaccinate the entire state of Massachusetts (6.4 million) within 6 days, vaccinating 80% of the population in the first 3 days and the remaining 20% in the next 3 days [23]. One interesting point of reference is the last mass vaccination campaign that occurred in the U.S. in 1947, which began after a man with undiagnosed hemorrhagic smallpox infected twelve others [7]. In this case, 6.35 million people in New York City were vaccinated between April 4 and May 2 [34] (although there is some debate as to the total number vaccinated [33]).

Yet another unknown is the fraction of infected people who would be able to be traced by the public health system. When modeling the Kosovo outbreak of 1972 that occurred in rural Yugoslavia, Gani and Leach assumed that 97.5% of infected population was traceable [10]. Given our modern, mobile world population, this percentage may be much lower.

3.2 INFECTION AND CONTACT TRACING

In this section, we present the equations that govern movement between unexposed and exposed states via "meetings" between susceptible and infectious people as well as environmental exposures ($\gamma \neq 0$). In addition, we also identify whether the meetings are traceable ($\theta_c \neq 0$) or not. Some equations deal only with identifying those individuals who have had a traceable meeting and will be subsequently contacted and either vaccinated or quarantined.

In the model, contact tracing is only applied to those who have not yet become symptomatic, namely people in states Uc, Ucv, Ec and Ecv. These states contain people that have had traceable meetings (as designated by the letter c in their state names) and will be contacted if and when contact tracing is initiated. Until such time, people in Ec and Ecv will simply progress to a symptomatic state as if they were in E or Ev. Similarly, people in Uc and Ucv will be just as susceptible to infection as people in U and Uv.

Below are the equations governing movement out of states U, Uv, Uc, Ucv, E and Ev. A schematic of these transitions is shown in Figure 1. For convenience, let the number of people who can infect others (that is, the number of infectious people not isolated) be

$$\tilde{I} = S + Sd, \tag{5}$$

and let the number of unexposed people susceptible to environmental exposure be

$$\tilde{U} = U + Uq + Uv + Uqv + Uc + Ucv. \tag{6}$$

The first four equations below represent traceable meetings with infectious people while the

last two equations represent untraceable meetings.

$$f(U, Uc) = \theta_c(1-\phi)\beta\,\tilde{I}\,U \tag{7}$$
$$f(Uv, Ucv) = \theta_c(1-\phi)\beta\,\tilde{I}\,Uv \tag{8}$$
$$f(U, Ec) = \theta_c\phi\beta\,\tilde{I}\,U \tag{9}$$
$$f(Uv, Ecv) = \theta_c\phi\beta\,\tilde{I}\,Uv \tag{10}$$
$$f(U, E) = (1-\theta_c)\phi\beta\,\tilde{I}\,U + \min(\frac{U}{\tilde{U}}\gamma, \frac{U}{\Delta t}) \tag{11}$$
$$f(Uv, Ev) = (1-\theta_c)\phi\beta\,\tilde{I}\,Uv + \min(\frac{Uv}{\tilde{U}}\gamma, \frac{Uv}{\Delta t}) \tag{12}$$

(Note that when this model is implemented, care must be taken when $\tilde{U}$ becomes small; this issue can be addressed by adding a small positive number to $\tilde{U}$, one on the order of floating point precision.)

Equations (13) and (14) below, which are similar to equations (11) and (12), represent infections that result from a meeting between an infectious person and an unexposed person who has had a prior meeting with an infectious person that was traceable. (Of course, this prior, traceable meeting did not result in infection as they are still in Uc and Ucv.)

$$f(Uc, Ec) = \phi\beta\,\tilde{I}\,Uc + \min(\frac{Uc}{\tilde{U}}\gamma, \frac{Uc}{\Delta t}) \tag{13}$$
$$f(Ucv, Ecv) = \phi\beta\,\tilde{I}\,Ucv + \min(\frac{Ucv}{\tilde{U}}\gamma, \frac{Ucv}{\Delta t}) \tag{14}$$

The equations below are similar to equations (7) and (8) but represent traceable meetings between infectious and already infected people.

$$f(E, Ec) = \theta_c\beta\,\tilde{I}\,E \tag{15}$$
$$f(Ev, Ecv) = \theta_c\beta\,\tilde{I}\,Ev \tag{16}$$

The equations below represent infections while in quarantine due to environmental exposure.

$$f(Uq, Eq) = \min(\frac{Uq}{\tilde{U}}\gamma, \frac{Uq}{\Delta t}) \tag{17}$$
$$f(Uqv, Eqv) = \min(\frac{Uqv}{\tilde{U}}\gamma, \frac{Uqv}{\Delta t}) \tag{18}$$

If $\gamma = 0$, then no one will become infected while in quarantine.

Expressions involving the $\min(\cdot,\cdot)$ function, which represent environmental exposures, also appear in equations (11)-(14), but not in the equations governing movement into Uc, Ucv, Ec and Ecv because movement into these states implies that the source of infection was traceable. In the current model, we assume that environmental exposures are not traceable. As a side note, environmental exposures may be traceable if a large number of people can be traced back to a single place where the exposure occurred. However, this is currently unlikely in a time frame

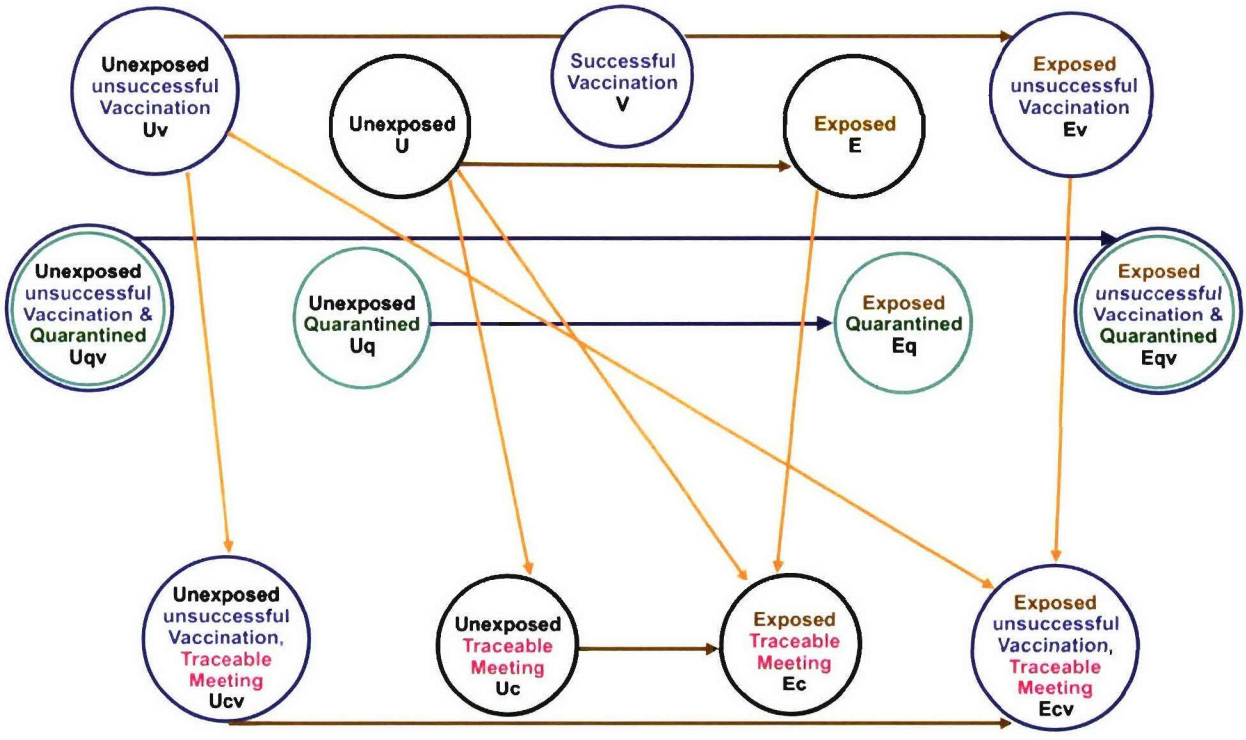

Figure 1. A schematic of the transitions between states due to infection and contact tracing. Movement of people who have had traceable meetings is indicated by an orange arrow, while movement of those who have been exposed via an untraceable meeting is indicated by a brown arrow. Note that although individuals in Uc and Ucv become infected via an untraceable meeting (hence, the brown arrows), they retain their "traceable" status and are moved into Ec and Ecv. Individuals in Uc and Ucv have had traceable contacts with an infectious person in the past; however, that contact did not lead to an infection. Finally, infections due solely to an environmental exposure ($\gamma \neq 0$) are indicated by a purple arrow. A blue circle indicates that those in this state have been vaccinated, while a green circle indicates that those in this state are in quarantine.

on the order of a week or so. A recent example of identifying a common source of exposure is the cluster of SARS cases at the Amoy Gardens Estate, where approximately 300 people were infected [30]. In this case, transmission appears to have been the result of both close contact and a leaking sewer system. It was contact tracing and subsequent analysis that led to the identification of a possible environmental source. Finally, the $\min(\cdot,\cdot)$ expression does not always yield an ODE. For example, when $(Uq/\Delta t) < \gamma(Uq/\tilde{U})$, the number of people leaving Uq and entering Eq is $f(Uq, Eq)\Delta t = (Uq/\Delta t)\Delta t = Uq$, which is not a differential equation.

3.3 SMALLPOX DISEASE PROGRESSION

The following equations govern movement from exposed states to symptomatic states:

$$f(E,S) = (1-\lambda)\alpha\, E \tag{19}$$
$$f(E,Sd) = \lambda\alpha\, E \tag{20}$$
$$f(Ec,S) = (1-\lambda)\alpha\, Ec \tag{21}$$
$$f(Ec,Sd) = \lambda\alpha\, Ec \tag{22}$$
$$f(Ev,S) = (1-\lambda)\alpha Ev \tag{23}$$
$$f(Ev,Sd) = \lambda\alpha\, Ev \tag{24}$$
$$f(Ecv,S) = (1-\lambda)\alpha\, Ecv \tag{25}$$
$$f(Ecv,Sd) = \lambda\alpha\, Ecv \tag{26}$$
$$f(Eq,Sq) = (1-\lambda)\alpha\, Eq \tag{27}$$
$$f(Eq,Sqd) = \lambda\alpha\, Eq \tag{28}$$
$$f(Eqv,Sq) = (1-\lambda)\alpha\, Eqv \tag{29}$$
$$f(Eqv,Sqd) = \lambda\alpha\, Eqv. \tag{30}$$

These equations distinguish between the fraction of those infected people that will recover, $(1-\lambda)$, and of those that will die, λ.

The following equations govern movement from symptomatic to the immune and dead states:

$$f(S,R) = \rho S \tag{31}$$
$$f(Sq,R) = \rho Sq \tag{32}$$
$$f(Sqt,R) = \rho_t Sqt \tag{33}$$
$$f(Sd,D) = \delta Sd \tag{34}$$
$$f(Sqd,D) = \delta Sqd \tag{35}$$
$$f(Sqtd,D) = \delta_t Sqtd. \tag{36}$$

As mentioned earlier, the infectious period is followed by a non-infectious recovery period, which is currently not modeled. The parameters ρ and δ determine the amount of time individuals are in S and Sd and allowed to spread disease. Thus, $R(t)$ is the number of individuals who have survived infection with immunity but who have not likely fully recovered yet. See Appendix A for equations that can be used to model the non-infectious recovery period.

3.4 OUTBREAK CONTROL POLICIES

Whether or not someone is vaccinated or quarantined during a particular time step (that is, $f(i,j) \neq 0$, where j is a state holding either vaccinated or quarantined people) depends on whether or not there is room in quarantine or vaccine available. See Appendix B for the scheme used to impose the resource limits defined in Table 6.

3.4.1 Quarantine and vaccination of non-symptomatics

In this section, we present the equations governing quarantine and vaccination of those not yet symptomatic. Since the vaccine efficacy window is estimated to be only about the first four days after exposure, we do not model the vaccination of those already symptomatic.

Whether people are vaccinated or quarantined depends on whether or not contact tracing has been initiated and whether quarantine capacity or vaccination supply limits have been reached. Quarantining individuals with no symptoms can only occur if they have been designated as traceable contacts ($\theta_c \neq 0$). We consider three possibilities: (1) both vaccination and quarantine, (2) only vaccination and (3) only quarantine.

Let $\tilde{V}$ be the populations in the model that may request and receive vaccination; that is,

$$\tilde{V} = U + E. \tag{37}$$

If both vaccination and quarantine can occur, then the following transition rates are used:

$$\begin{aligned}
f(U,V) &= \epsilon_u \min(\frac{U}{\tilde{V}}\nu, U) && (38)\\
f(E,V) &= \epsilon_e \min(\frac{E}{\tilde{V}}\nu, E) && (39)\\
f(U,Uv) &= (1-\epsilon_u) \min(\frac{U}{\tilde{V}}\nu, U) && (40)\\
f(E,Ev) &= (1-\epsilon_e) \min(\frac{E}{\tilde{V}}\nu, E) && (41)\\
f(Uc,V) &= \epsilon_u Uc && (42)\\
f(Ec,V) &= \epsilon_e Ec && (43)\\
f(Uc,Uqv) &= (1-\epsilon_u) Uc && (44)\\
f(Ec,Eqv) &= (1-\epsilon_e) Ec && (45)\\
f(Ucv,Uqv) &= Ucv && (46)\\
f(Ecv,Eqv) &= Ecv. && (47)
\end{aligned}$$

A schematic of these transitions is shown in Figure 2. In this case, when people move to quarantine, they are also vaccinated if they have not been vaccinated already. Equations (42)-(45) model vaccination as a result of contact tracing.

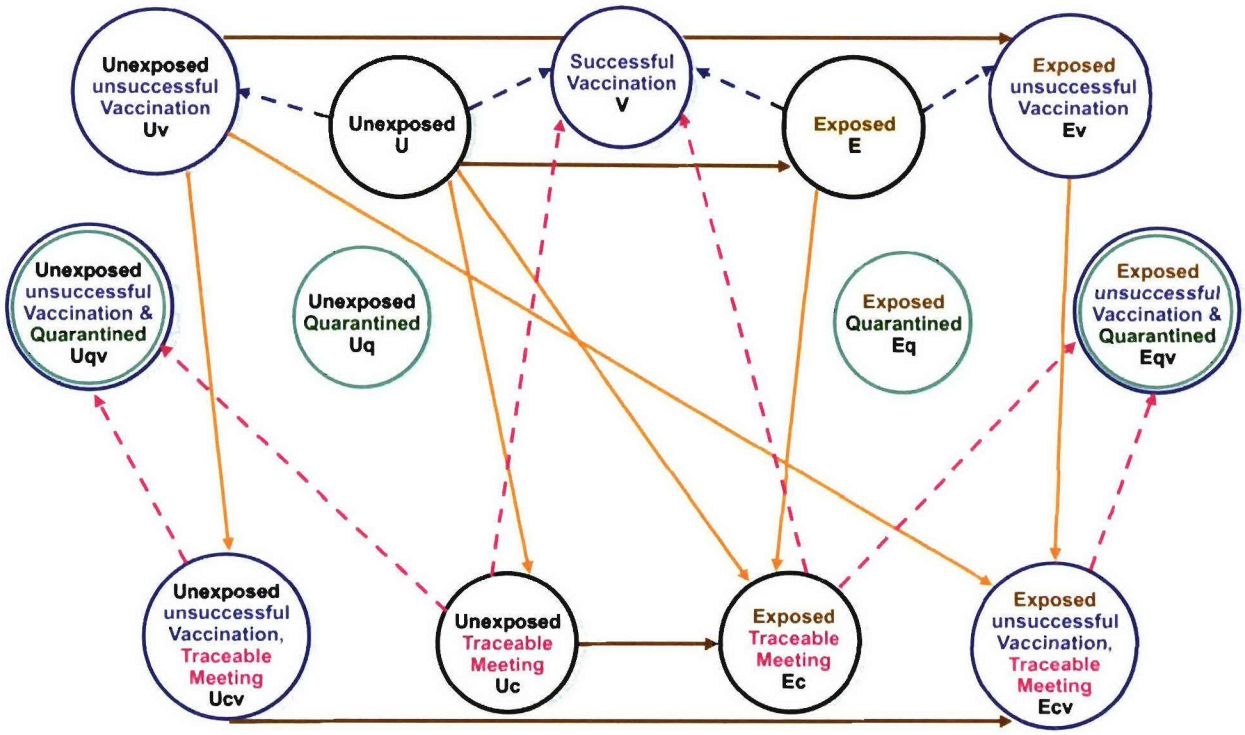

Figure 2. A schematic of the transitions allowed when mass vaccination and contact tracing are instituted to control an epidemic. The dashed arrows indicate that movement will only be allowed if there is sufficient capacity. The blue arrows indicate movement due to the mass vaccination protocol. The pink arrows indicate movement due to contact tracing. Successfully vaccinated individuals resulting from contact tracing or from the mass vaccination campaign move into V. (To place these transitions in context, we've also shown connections between the states representing new infections and identification of those who would be contacted if contact tracing were initiated. As in Figure 1, brown arrows indicate movement of those who have been exposed via an untraceable meeting, while movement of those who have had a traceable meeting is indicated by an orange arrow.) The color coding of the circles is the same one used in Figure 1.

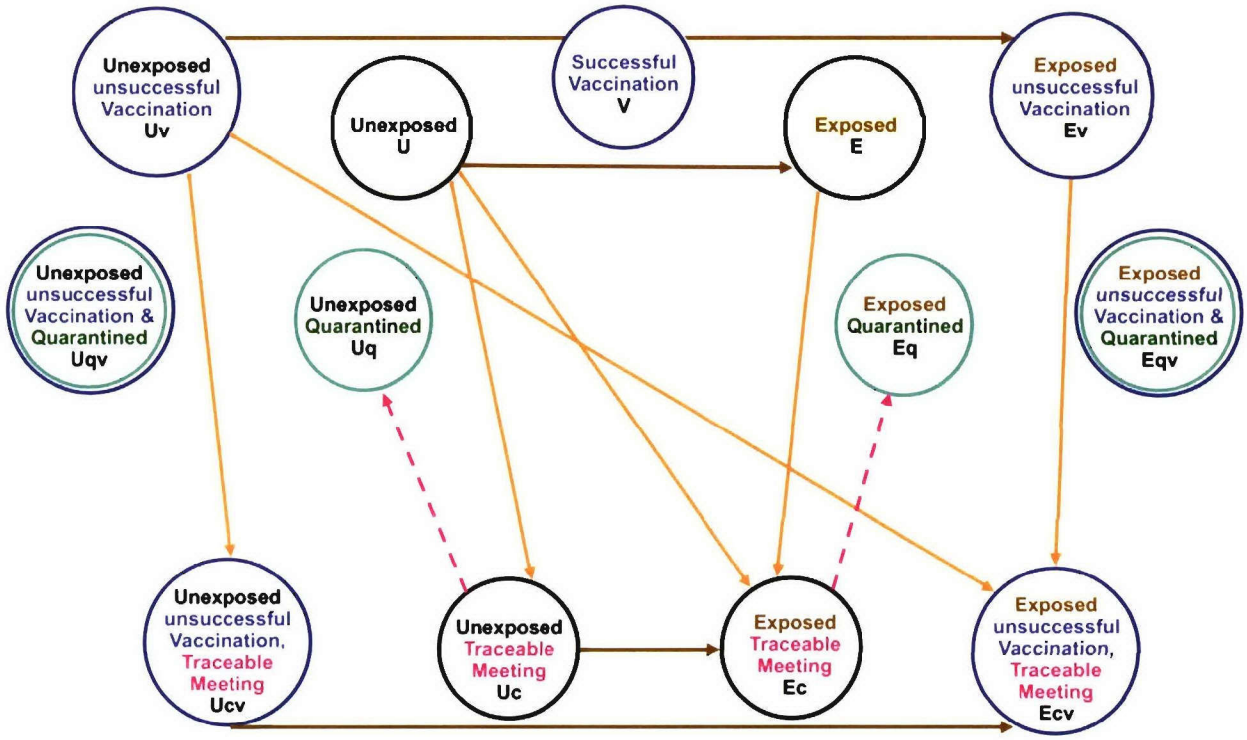

Figure 3. A schematic of the transitions allowed when contact tracing is followed by quarantine. The color coding of the arrows and circles is the same as that in Figure 2; pink arrows indicate transitions due to contact tracing and quarantining if there is capacity.

If only vaccination can occur, then equations (52)-(43) and the equations below are used.

$$f(Uc, Ucv) = (1 - \epsilon_u)Uc \tag{48}$$
$$f(Ec, Ecv) = (1 - \epsilon_e)Ec. \tag{49}$$

In this case, equations (42), (43) and the two above model vaccination as a result of contact tracing. (In the experiments to follow, we assume that quarantine space is unlimited.)

If only quarantining can occur, then equations (52)-(55), (46), (47) and the equations below are used.

$$f(Uc, Uq) = Uc \tag{50}$$
$$f(Ec, Eq) = Ec \tag{51}$$

A schematic of these transitions is shown in Figure 3.

In all cases, people move out of the quarantine after an average of σ^{-1} days:

$$f(Uq, U) = \sigma Uq \quad (52)$$
$$f(Uqv, Uv) = \sigma Uqv \quad (53)$$
$$f(Eq, E) = \sigma Eq \quad (54)$$
$$f(Eqv, Ev) = \sigma Eqv, \quad (55)$$

where σ^{-1} should be greater than α^{-1}, the incubation period, so that those who are infected and in quarantine will not be released back into the general population but rather will become sick while in quarantine and thus be held there.

3.4.2 Isolation and treatment of symptomatics

Other rates (or $f(i, j)$) may be nonzero due to isolation and treatment of symptomatic people. Once the epidemic control policies are initiated, we assume that symptomatic people will be isolated with an average delay of θ_s^{-1} days between symptom onset and isolation. If there is no treatment available and symptomatic people can only be isolated, then the following rates are used:

$$f(S, Sq) = \theta_s S \quad (56)$$
$$f(Sd, Sqd) = \theta_s Sd. \quad (57)$$

If we are modeling an infectious disease for which there is treatment and unfilled capacity, then the following rates are used:

$$f(S, Sqt) = \theta_s S \quad (58)$$
$$f(Sq, Sqt) = Sq \quad (59)$$
$$f(Sd, Sqt) = \theta_s(1 - \tilde{\lambda})\, Sd \quad (60)$$
$$f(Sd, Sqtd) = \theta_s \tilde{\lambda}\, Sd \quad (61)$$
$$f(Sqd, Sqt) = (1 - \tilde{\lambda})\, Sqd \quad (62)$$
$$f(Sqd, Sqtd) = \tilde{\lambda}\, Sqd, \quad (63)$$

where $\tilde{\lambda} = \lambda_t/\lambda$ is the ineffectiveness of the treatment. Currently, if only supportive care is given to smallpox patients, then we assume that $\lambda_t = \lambda$; that is, mortality remains constant despite treatment. However, antiviral drugs are being developed [12, 19]. Also, we assume that the mean transition time to enter treatment while in isolation is 1 day (implied by the lack of the factor θ_s in some of the equations above).

3.5 MODEL RESULTS

3.5.1 Model validation: comparison to Kosovo 1972

To validate our model, we compare the output of the model (number of cases) to data from the Kosovo outbreak of 1972 [7, 21], for which the global eradication strategy was implemented.

We used the parameters given in Tables 3-5, except those shown in Table 7, and we place no limits on the amount of vaccine available (daily or total) or quarantine space. The initial conditions are $E_0 = 1$, $N_t = 2.2$ million people [7]. In addition, we set $M_t = 0$, that is, no simulation of treatment during the symptomatic infectious period.

TABLE 7

Parameters for the 1972 smallpox outbreak in Kosovo

Parameter	Notation	Value
time elapsed before response is initiated (days)	κ	45.5
number of individuals given prophylaxis per day	ν	(1-ϵ_h)(N_t/45)
general population ("herd") immunity	ϵ_h	0.50 [10]
fraction of contacts traced	θ_c	0.975 [10]
daily prophylaxis available	M_v	ν
total prophylaxis available	M_{vtotal}	N_t (unlimited)
daily new contact quarantine capacity	M_q	N_t (unlimited)
daily total contact quarantine capacity	M_{qtotal}	N_t (unlimited)
daily treatment capacity	M_t	0

On March 16 vaccinations in Kosovo began, two days after smallpox was suspected in 4 patients [7], 45 days after the index case is estimated to have become infected (κ= 45.5 days). By the end of April, after about 45 days, nearly 95% of the population of Kosovo ($N_t = 2.2$ million) was vaccinated, implying an average vaccination rate of ($N_t/45$) people/day [7]. This rate corresponds to a rate of $(1 - \epsilon_h)(N_t/45)$ non-immune people/day, given the initial placement of $\epsilon_h N_t$ people in V to simulate 'herd' immunity ($V_0 = \epsilon_h N_t$ and $U_0 = (1 - \epsilon_h)N_t - E_0$).

As shown in Figure 4, there is good agreement between the recorded number of symptomatic individuals and the number predicted by the model for $R_0 = 10$. If we increase R_0 to 10.2, we get a better fit to the number of symptomatic cases between 50 and 70 days; however, doing so leads to an overestimation of the cumulative number of cases.

Although the model does not capture the typical waves of cases or generations of illness, we see that the ODEs do capture the average transition time. For example, we see that the index case becomes sick after approximately 15 days.

As shown by the data, the incubation period of smallpox appears to follow a unimodal distribution rather than an exponential one, which necessarily underlies the ODE that governs this transition. This is one reason to move to a slightly more complicated model that can use general probability distribution functions (not just exponential ones) to define the transitions between the states.

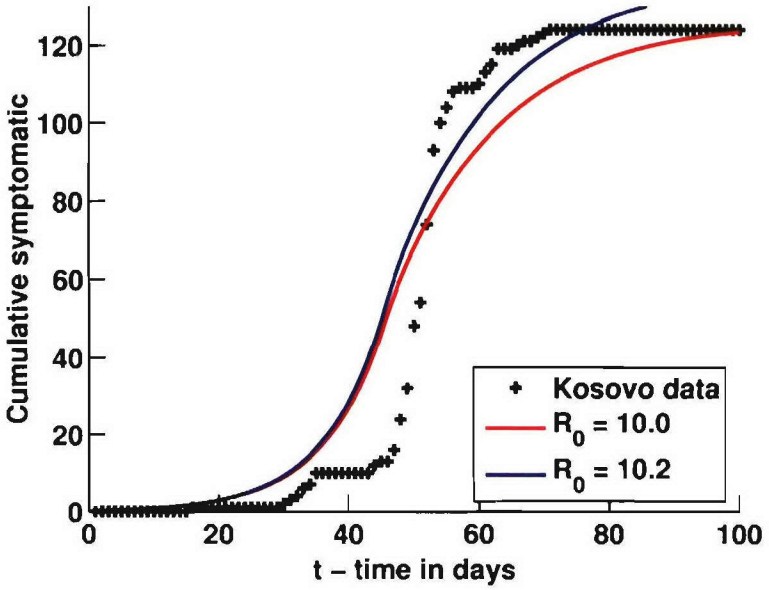

Figure 4. A comparison of the number of cases from the 1972 Kosovo outbreak and number of cases predicted by the ODE model when there is a 45.5-day delay in initiating the control policy. Depending on the value of R_0 the model can be made to fit the steep increase in cases ($R_0 = 10.2$) or the cumulative number of cases ($R_0 = 10.0$).

3.5.2 Hypothetical contemporary outbreak

To simulate a contemporary outbreak, we used the parameters given in Tables 3-5 except those shown in Table 8. We consider an initial release of smallpox that infects 100 people ($E_0 = 100$) out of a total population of $N_t = 3$ million people, which is approximately the number of people in the Boston metropolitan area, and we place no limits on the amount of vaccine available (daily or total) or quarantine space. (See Appendix C for the combinations of the parameters required to model the public health responses.)

If the U.S. health care system responds as the one in Kosovo did, that is, during the second generation of secondary cases, then the model estimates that there will be roughly 106,600 cases and over 31,800 deaths, as shown by the red curves in Figures 5 and 6. The second generation of cases would be expected to surface around day 45 because of the assumed average incubation period of 14.6 days. (The first cases will appear around day 15, the first generation of secondary cases around day 30, and the second generation of secondary cases around day 45.) If the public health system is able to diagnose and respond after the first few cases, but before the first generation of cases, then the number of cases and deaths will be bounded by the green and the blue curves. On the other hand, if we were able to detect and then initiate a response once the first case appears, then the model estimates there will be about 890 cases and roughly 270 deaths.

Figure 7 shows that the number of people in quarantine peaks soon after the control policies

TABLE 8

Parameters for a contemporary smallpox outbreak

Parameter	Notation	Value
time elapsed before response is initiated (days)	κ	15, 30, 45
number of individuals given prophylaxis per day	ν	100,000 ($N_t/10^6$) [28]
fraction of contacts traced	θ_c	0.20
daily prophylaxis available	M_v	ν
total prophylaxis available	M_{vtotal}	N_t (unlimited)
daily new contact quarantine capacity	M_q	N_t (unlimited)
daily total contact quarantine capacity	M_{qtotal}	N_t (unlimited)
daily treatment capacity	M_t	0

are implemented, as expected. On the other hand, the number of symptomatics peaks many days (a few more than the incubation period) after the policies are implemented, as shown in Figure 8.

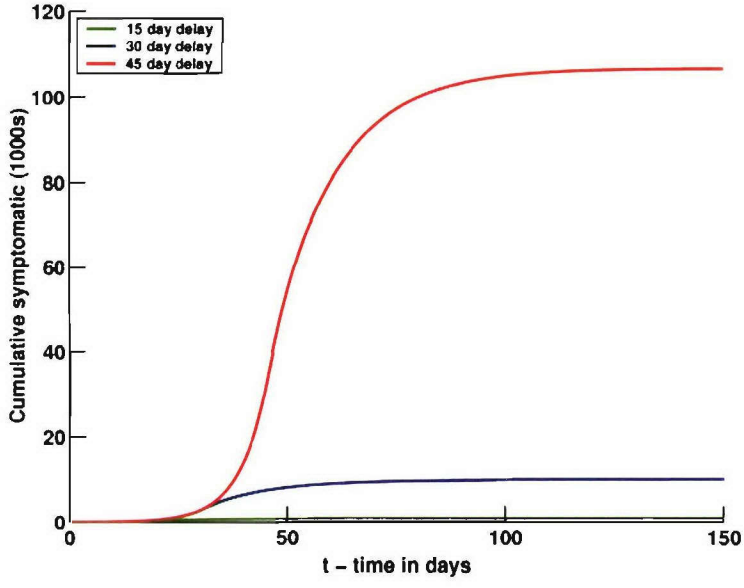

Figure 5. The cumulative number of people infected during the contemporary smallpox outbreak, $\tilde{S}(t) = S(t) + Sd(t) + Sq(t) + Sqd(t) + R(t) + D(t)$.

Figure 9 shows the number of deaths for each of the response delays considered and for each control policy: (1) the combined policy (contact tracing with $\theta_c = 0.20$ and mass vaccination at a rate of 100,000 people/day per 1 million people), (2) mass vaccination alone, (3) contact tracing

alone with a very optimistic value for the percentage of infected people found ($\theta_c = 0.90$), and (4) contact tracing with a much lower value for the percentage of infected people found ($\theta_c = 0.20$).

As shown, if a response is initiated very shortly after the first case appears, then there is not much difference between the four policies considered, but a mass vaccination campaign would likely result in more vaccine-related deaths (which is currenlty not modeled). The number of vaccine-related deaths is expected to be 1 to 2 per million people vaccinated [22]. However, rapidly identifying and tracing the initial cases infected during an attack, who are not yet symptomatic or just becoming symptomatic, might be difficult without biosensors. As delay increases, mass vaccination and the combined policy are equally effective at controlling the epidemic.

Finally, it should be noted that the contact tracing rate will likely be limited; this is not simulated in the model. In addition, random effects at the beginning of an epidemic are not modeled by this deterministic model [8] nor are social networks, which may facilitate contact tracing.

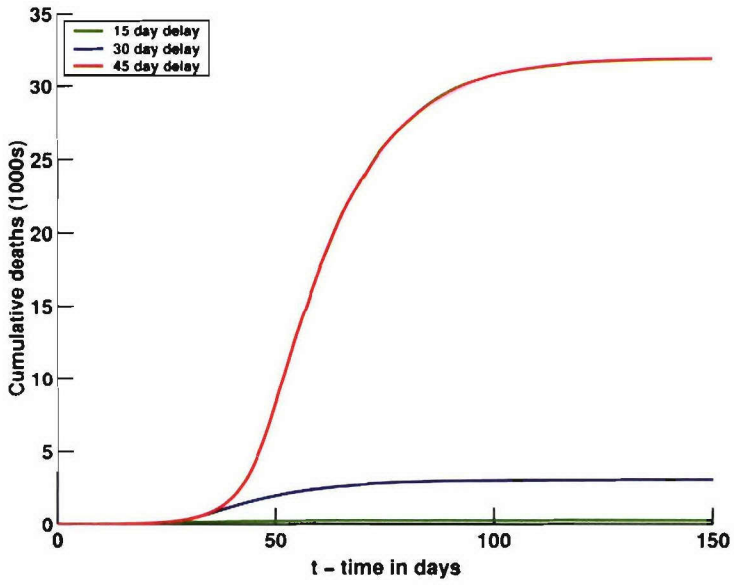

Figure 6. The cumulative number of deaths resulting from the contemporary outbreak, $D(t)$.

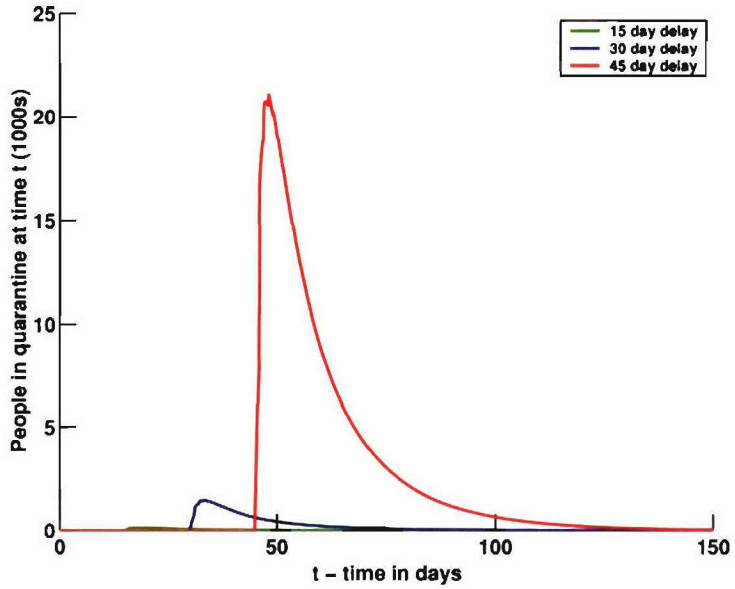

Figure 7. The number of people in quarantine (not including symptomatic people) during the contemporary outbreak, $\bar{Q}(t) = Eq(t) + Uq(t) + Eqv(t) + Uqv(t)$.

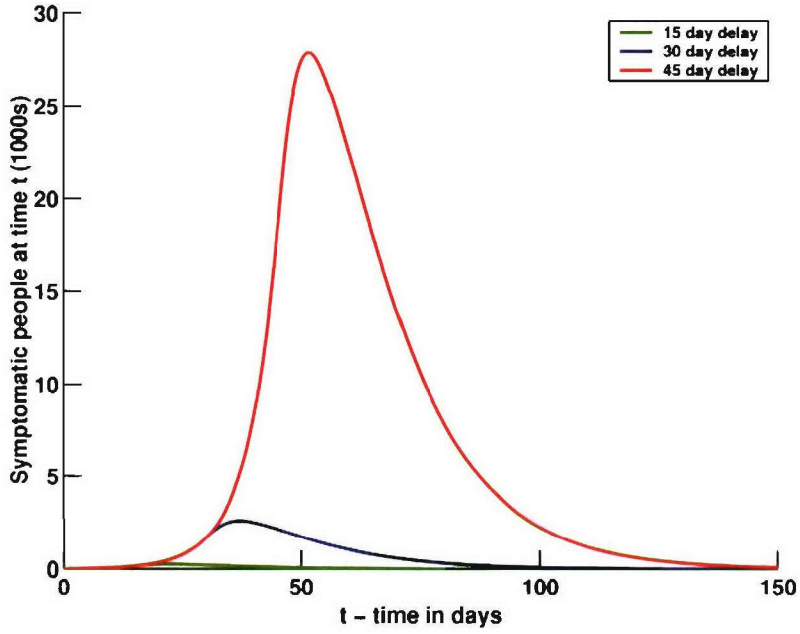

Figure 8. The number of symptomatic people during the contemporary outbreak, $\hat{S}(t) = S(t) + Sd(t) + Sq(t) + Sqd(t)$.

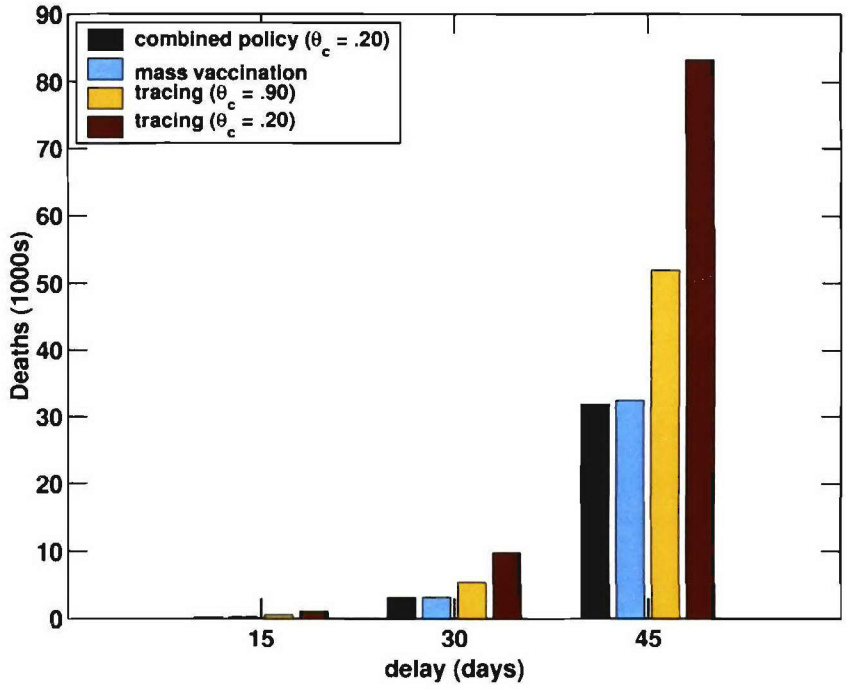

Figure 9. A comparison of the number of deaths given three different smallpox control policies. For the policy of contact tracing alone, we considered two different values for θ_c, 0.20 and 0.90. For each policy, the deaths for a 15-day delay are under 1,000; they are 269, 270, 502, and 944 with respect to order shown in the legend.

4. A MODEL FOR INHALATION ANTHRAX

Inhalation anthrax is a noncontagious disease that we have modeled using three stages (a prodromal period, a brief "recovery" period, and then fulminant illness) to which different medical treatments and capacities may be applied. This model is different from the contagious disease model in that (1) there are no quarantine or contact states and (2) there are multiple stages of the disease. In addition, for smallpox, individuals are protected from infection by vaccination; for anthrax, individuals would likely be given a 60-day supply of prophylactic antibiotics, such as ciprofloxacin [15].

In this model, the six primary population states are categorized according to whether a person is unsuccessfully given prophylaxis (v), receiving treatment (t), will recover (r), or will die (d). Table 9 lists the nineteen states. Figure 10 shows a complete state diagram for this model, which is reflected by the transition rates defined in sections 4.2 and 4.3.

TABLE 9

States of the inhalation anthrax model

Disease States	Notation: Categorized Disease States					
Unexposed	$U(t)$	$Uv(t)$				
Exposed	$E(t)$	$Ev(t)$				
Symptomatic stage 1	$S1r(t)$	$S1(t)$	$S1vr(t)$	$S1v2(t)$	$S1tr(t)$	$S1t2(t)$
Symptomatic stage 2	$S2(t)$	$S2tr(t)$	$S2t3(t)$			
Symptomatic stage 3	$S3(t)$	$S3tr(t)$	$S3td(t)$			
Immune	$V(t)$					
Recovered	$R(t)$					
Dead	$D(t)$					

Individuals with inhalation anthrax initially experience nonspecific flu-like symptoms for a period of days and then sudden fever, labored breathing, and shock over a time period as short as a few hours, followed by death. However, it has been noted that there often appears to be a brief period of recovery before the final stage [17]. In this model, stage 1 represents the initial nonspecific flu-like stage; stage 2, the brief recovery period between the prodromal and fulminant stages; and stage 3, the fulminant and final stage.

When creating the model, we assumed that prodromal patients will receive the same prophylaxis as that given to patients with no symptoms. Thus, unexposed, exposed and prodromal people draw off the prophylaxis supply. To prevent so-called double counting or someone receiving prophylaxis before and after they become symptomatic, we define states $S1v$ and $S1vr$. If individuals have received prophylaxis when they are latent (infected but not symptomatic), but it was not successful (that is, they are in Ev), they are prevented from receiving additional prophylaxis by

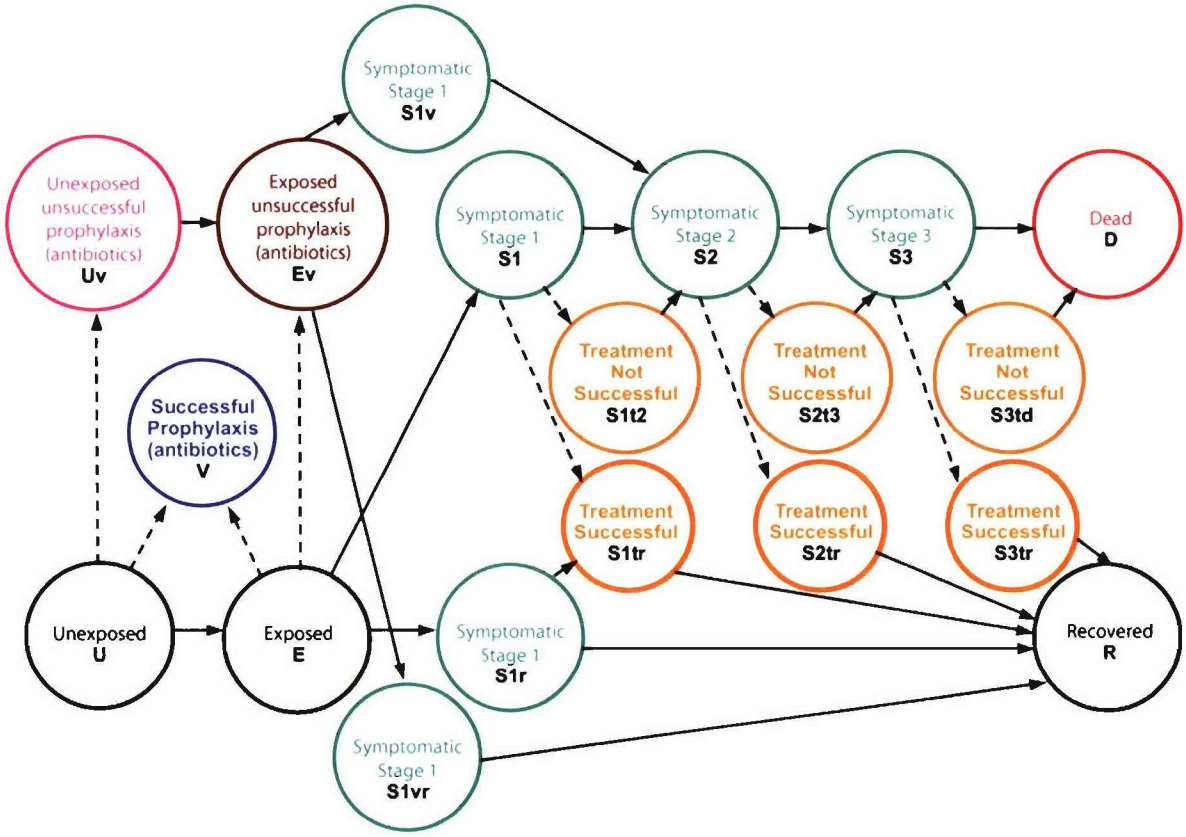

Figure 10. A schematic of the transitions between states of the anthrax model. The dashed arrows indicate that movement will only occur if related resource limits have not been exceeded.

moving them into $S1v$ and $S1vr$ rather than $S1$ and $S1r$. See Appendix D for an alternate version of the model in which the prodromal treatment is independent of prophylaxis supply and rate of distribution.

Currently, the model does not consider the dependence of the incubation period and other parameters on the dose of anthrax received. The model could be updated to include a number of "levels" of illness corresponding to various levels of dose received, thus requiring additional disease parameters, but at the moment there is relatively little data from animal studies to support such a model.

4.1 PARAMETERS OF THE INHALATION ANTHRAX MODEL

The parameters can be grouped into four categories: (1) disease progression, (2) prophylaxis efficacy, (3) public health response, and (4) resource limits, as shown in Tables 10-12. Most of

the disease progression parameters, shown in Table 10, were defined based on data from the most recent inhalation anthrax cases in 2001.

We chose an average incubation time of 4.5 days [17]. The incubation periods that could be estimated from the most recent cases are shown in Figure 11. It is possible that longer incubation periods would have been observed in 2001 if antibiotic prophylaxis had not been distribued to the at-risk population [3,4]. Much longer incubation periods were observed during the 1979 Sverdlovsk outbreak [13, 26] as shown in Figure 11. The average incubation period of this outbreak was 12.2 days, which is longer than estimates of 1 to 6 days for "high-dose exposures" [31]. Potential explanations for the longer incubation times are delayed germination of spores [13, 26], low dose exposure [31], and reaerosolization of spores.

TABLE 10

Inhalation anthrax disease progression parameters

Parameter	Notation	Value
incubation period (days)	α^{-1}	1-7 [5]
untreated mortality	λ	historically 0.89 [13]
untreated recovery time (days)	ρ^{-1}	25.1 [17, 26]
length of stage 1 (days)	δ_1^{-1}	3.5 [17]
length of stage 2 (days)	δ_2^{-1}	1.5
length of stage 3 (days)	δ_3^{-1}	0.5
treatment inefficacy, stage 1	$\tilde{\lambda}_1$	0.45 [17]
treatment inefficacy, stage 2	$\tilde{\lambda}_2$	0.95
treatment inefficacy, stage 3	$\tilde{\lambda}_3$	0.99
treated recovery time, stage 1 (days)	$\rho_{t_1}^{-1}$	22.3 [17]
treated recovery time, stage 2 (days)	$\rho_{t_2}^{-1}$	23.3
treated recovery time, stage 3 (days)	$\rho_{t_3}^{-1}$	24.3
treated length of stage 1 (days)	$\delta_{t_1}^{-1}$	3.5
treated length of stage 2 (days)	$\delta_{t_2}^{-1}$	1.5
treated length of stage 3 (days)	$\delta_{t_3}^{-1}$	0.5

According to the 2001 data, patients took approximately 3.5 days on average to go to their doctor after becoming sick [17]. Thus, we estimated the initial stage to last about 3.5 days, which is in keeping with the CDC fact sheet, which states 1 to 5 days [5].

To define the remaining disease progression parameters for untreated individuals, we used the data for the two patients who were sent home without receiving antibiotics and who later returned to the emergency room with fulminant illness, dying after 1 and 3 days after their initial visits. For these patients, an average of 5.5 days passed between onset and death. Thus, we estimate the average length of the last 2 stages to be 2 days. Since stage 3 is relatively short, we define the

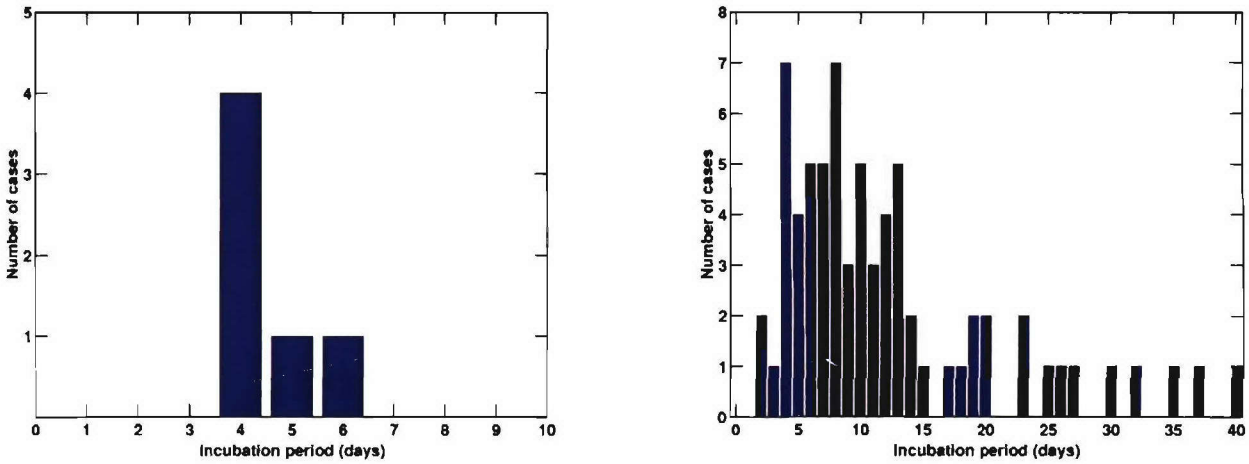

Figure 11. On the right are the incubation periods of the 2001 U.S. outbreak that could be estimated [17]. On the left are the observed incubation periods of the 1979 Sverdlovsk outbreak [26].

duration of stage 2 to be 1.5 days and the duration of stage 3 to be 0.5 days. We define untreated recovery time to be 25.1 = 21 [26] + 4.1 [17] days for stage 1. For stages 2 and 3, we increased this recovery time by 1 and 2 days, respectively. We assume that unsuccessful treatment does not shorten nor lengthen the duration of the symptomatic disease stages.

Table 11 shows the assumed prophylaxis efficacy. We assume an efficacy of 90% when prophylaxis is started during the incubation period. Significant protection against death was achieved with prophylactic antibiotics for Rhesus monkeys before discontinuation of the antibiotics 30 days post-exposure [9]. However, it is not likely that there will be 100% compliance in the completion of a 60-day course of antibiotics [35]. Among the 2,000 postal workers that were advised to take prophylactic antibiotics for 60 days, it is estimated that only about 40% of them completed the full course of antibiotics [16].

The response parameters considered in this model are shown in Table 12. These parameters include response delay, prophylaxis distribution rate, and average time delay to enter treatment. In addition, capacity limits can be imposed on the treatment states. These limits are shown in Table 13.

TABLE 11

Inhalation anthrax prophylaxis efficacy

Parameter	Notation	Value
prophylaxis efficacy when uninfected	ϵ_u	0.90 [9, 35]
prophylaxis efficacy when infected	ϵ_e	0.90 [9, 35]

TABLE 12

Inhalation anthrax public health response parameters

Parameter	Notation	Value
time elapsed before response is initiated (days)	κ	varied
individuals given prophylaxis per day	ν	varied
average time delay to enter treatment (days)	θ_s^{-1}	1

TABLE 13

Resource limits for an anthrax outbreak

Parameter	Notation
daily prophylaxis capacity	M_v
total prophylaxis capacity	M_{vtotal}
daily treatment capacity, stage 2	M_{t_2}
daily treatment capacity, stage 3	M_{t_3}

4.2 INHALATION ANTHRAX DISEASE PROGRESSION

If all infections occur within a short time period, for example, a few hours, then it is reasonable to define the number of exposed people by the initial condition, $E(t_0) = E_0$, rather than modeling their movement from unexposed to exposed, as we did for smallpox. Since we are considering an aerosol release of anthrax, this is the approach we took.

We begin by defining the transition rates from exposed to symptomatic:

$$f(E, S1) = \lambda\alpha\, E \tag{64}$$
$$f(E, S1r) = (1-\lambda)\alpha\, E \tag{65}$$
$$f(Ev, S1) = \lambda\alpha\, Ev \tag{66}$$
$$f(Ev, S1r) = (1-\lambda)\alpha Ev. \tag{67}$$

Once symptomatic, without treatment, the disease progresses according to these equations:

$$f(S1r, R) = \rho\, S1r \tag{68}$$
$$f(S1, S2) = \delta_1\, S1 \tag{69}$$
$$f(S2, S3) = \delta_2\, S2 \tag{70}$$
$$f(S3, D) = \delta_3\, S3 \tag{71}$$

With treatment, the disease either progresses or results in recovery according to these equations:

$$f(S1tr, R) = \rho_{t_1} S1tr \quad (72)$$
$$f(S1t2, S2) = \delta_{t_1} S1t2 \quad (73)$$
$$f(S2tr, R) = \rho_{t_2} S2tr \quad (74)$$
$$f(S2t3, S3) = \delta_{t_2} S2t3 \quad (75)$$
$$f(S3tr, R) = \rho_{t_3} S3tr \quad (76)$$
$$f(S3td, D) = \delta_{t_3} S3td \quad (77)$$

4.3 MEDICAL INTERVENTIONS

In this section, we define the transition rates related to prophylaxis distribution and treatment. These rates are non-zero as long as the resource limits have not been reached. Let $\tilde{V}$ be the states in the model that may request and receive prophylaxis; that is,

$$\tilde{V} = U + E + S1 + S1r. \quad (78)$$

If the prophylaxis supply (daily or total) has not been reached, then the following equations rates model successful and unsuccessful administration of prophylaxis to those unexposed, latent and prodromal.

$$f(U, V) = \epsilon_u \min(\frac{U}{\tilde{V}}\nu, \frac{U}{\Delta t}) \quad (79)$$
$$f(U, Uv) = (1 - \epsilon_u) \min(\frac{U}{\tilde{V}}\nu, \frac{U}{\Delta t}) \quad (80)$$
$$f(E, V) = \epsilon_e \min(\frac{E}{\tilde{V}}\nu, (1 - \alpha)\frac{E}{\Delta t}) \quad (81)$$
$$f(E, Ev) = (1 - \epsilon_e) \min(\frac{E}{\tilde{V}}\nu, (1 - \alpha)\frac{E}{\Delta t}) \quad (82)$$

$$f(S1r, S1tr) = \min(\frac{S1r}{\tilde{V}}\nu, (1 - \rho)\frac{S1r}{\Delta t}) \quad (83)$$
$$f(S1, S1tr) = (1 - \tilde{\lambda_1}) \min(\frac{S1}{\tilde{V}}\nu, (1 - \delta_1)\frac{S1}{\Delta t}) \quad (84)$$
$$f(S1, S1t2) = \tilde{\lambda_1} \min(\frac{S1}{\tilde{V}}\nu, (1 - \delta_1)\frac{S1}{\Delta t}) \quad (85)$$

Equations (86) and (87) define the rate at which those in stage 2 and 3 enter treatment that will ultimately lead to recovery.

$$f(S2, S2tr) = (1 - \tilde{\lambda_2})\theta_s S2 \quad (86)$$
$$f(S3, S3tr) = (1 - \tilde{\lambda_3})\theta_s S3 \quad (87)$$

Equations (88) and (89) define the rate at which those in stage 2 and 3 enter treatment that will not stop the disease progression.

$$f(S2, S2t3) = \tilde{\lambda}_2 \theta_s S2 \quad (88)$$

$$f(S3, S3td) = \tilde{\lambda}_3 \theta_s S3 \quad (89)$$

4.4 RESULTS FOR A LARGE-SCALE AEROSOL ANTHRAX ATTACK

The model was used to investigate the effect of delaying prophylaxis and treatment. Of course, the effect of delay can be heightened or lessened by decreasing or increasing the average incubation time, respectively. We chose an average incubation time of 4.5 days, based on the most recent cases [17]. However, as mentioned, the Sverdlovsk outbreak did have a longer average incubation time [13, 26].

For the large-scale attack, an initial number of exposed people was determined using an HPAC (Hazard Prediction and Assessment Capability[1]) simulation of a brief line release of anthrax from a boat travelling in Boston Harbor, assuming wind from the south east. In the simulation, 1 kg of anthrax was released in 16 minutes. The simulation reported that approximately 510,000 people within the greater Boston area would be exposed (that is, receive a dose greater than or equal to LCt2, a dose lethal for greater than 2% of those exposed) with an average mortality of 61%. Thus, we assume that 510,000 people are infected ($E_0 = 510,000$) and that $\lambda = 0.61$.

TABLE 14

Parameters specific to the hypothetical anthrax attack

Parameter	Notation	Value
incubation period (days)	α^{-1}	4.5 [17]
untreated mortality	λ	0.61
daily prophylaxis capacity	M_v	100,000 - 750,000
total prophylaxis capacity	$M_{v\,total}$	N_t (unlimited)
daily treatment capacity, stage 2	M_{t_2}	0.50(16,600 [32])
daily treatment capacity, stage 3	M_{t_3}	600 [1]

Next, we must define the number of people who will not become sick but will demand prophylaxis, U_0. If we define this number to be small, say 50,000, this corresponds to accurately identifying those exposed and preferentially treating them, that is, having very accurate knowledge of the shape of the plume as a function of time and those people in the plume area at that time. However, if there is no way to determine this information, then with so many people becoming sick, it is likely that the entire metropolitan population will seek prophylaxis, and the total number of

[1] http://www.dtra.mil/Toolbox/Directorates/td/programs/acec/hpac.cfm

people in the simulation who will demand prophylaxis should be reflective of the number of people in the metropolitan area ($N_t = 3,000,000$, $U_0 = N_t - E_0$).

For this scenario, we use the parameters shown in Tables 10-12, except for those shown in Table 14. We define the capacity limit for those in stage 2 (M_{t_2}) to be a percentage of the number of hospital beds in Massachusetts, which is estimated to be 16,600 [32]; we assume that 50% of these beds can be made available to patients needing advanced care. The capacity limit for stage 3 (M_{t_3}) is estimated by the number of ventilators (portable and stationary) in the push packs delivered to New York City on September 11th [1]; we assume that existing ventillators in the city will already be in use. It should be noted that the capacity for stage 2 and stage 3 treatments are not drivers of the attack outcome because the efficacy of these treatments are so low.

Figures 12 and 13 show the total number of deaths and symptomatic people as a function of delay in public health response, which is primarily distribution of prophylaxis. Each pair of colored curves corresponds to a different distribution rate (ν). Figure 12 shows that as treatment is delayed, the number of symptomatic people approaches the number of those exposed, while Figure 13 shows that as delay increases the number of deaths approaches 311,300 people (or λE_0).

In addition, from these figures we can see that the number of cases and deaths is also dependent on the prophylaxis demand. During the incubation period, those exposed and unexposed will be indistinguishable from each other, so that if many uninfected people demand prophylaxis, then those who are infected will not receive prophylaxis in the most timely fashion possible. Overall, the sooner medical interventions are provided and the higher the distribution rate, the greater the reduction in deaths.

Assuming a higher prophylaxis efficacy, for example, 95% due to higher compliance or more effective prophylaxis, does not have much of an effect on the number of cases and deaths if prophylaxis must be distributed to the metropolitan population. Figures 14 and 15 show the predicted numbers of cases and deaths assuming 95% efficacy. There is a greater difference between the 95% and 90% prophylaxis efficacy when plume mapping can be used to target prophylaxis distribution (dashed curves).

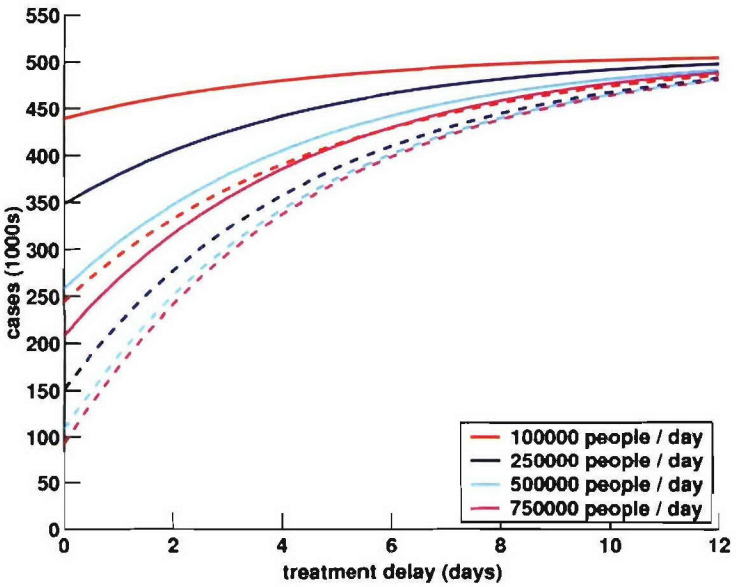

Figure 12. The number of symptomatic people as a function of delay in initiating a public health response, assuming a prophylaxis efficacy of 90%. This figure shows four possible distribution rates for prophylaxis. Solid lines correspond to the assumption that the metropolitan region will seek prophylaxis, while the dashed lines correspond to only those in the plume plus an extra 50,000 people demanding prophylaxis.

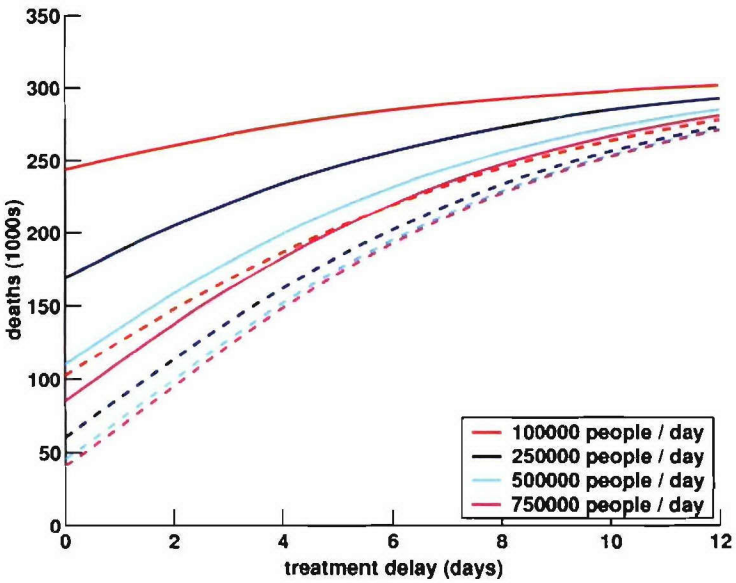

Figure 13. The number of deaths as a function of delay in initiating a public health response, assuming a prophylaxis efficacy of 90%. The curves are colored-coded according to prophylaxis distribution rate as in Figure 12.

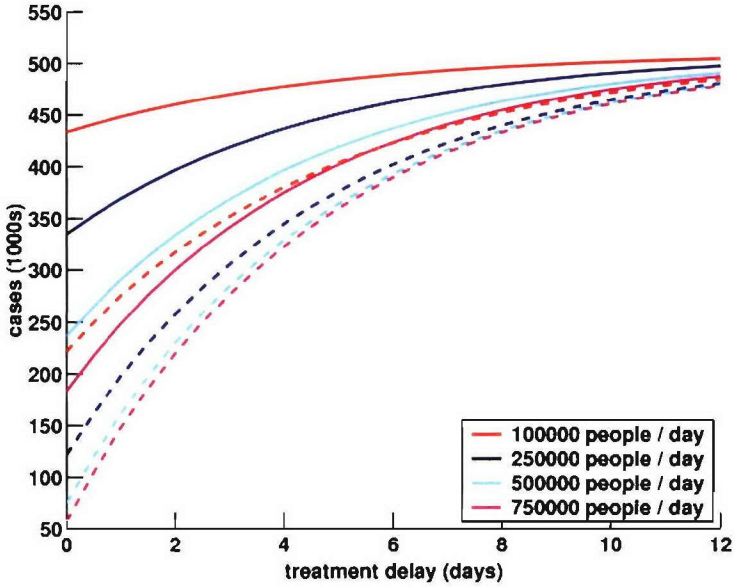

Figure 14. The number of symptomatic people as a function of delay in initiating a public health response, assuming a prophylaxis efficacy of 95%. The curves are colored-coded according to prophylaxis distribution rate as in Figure 12.

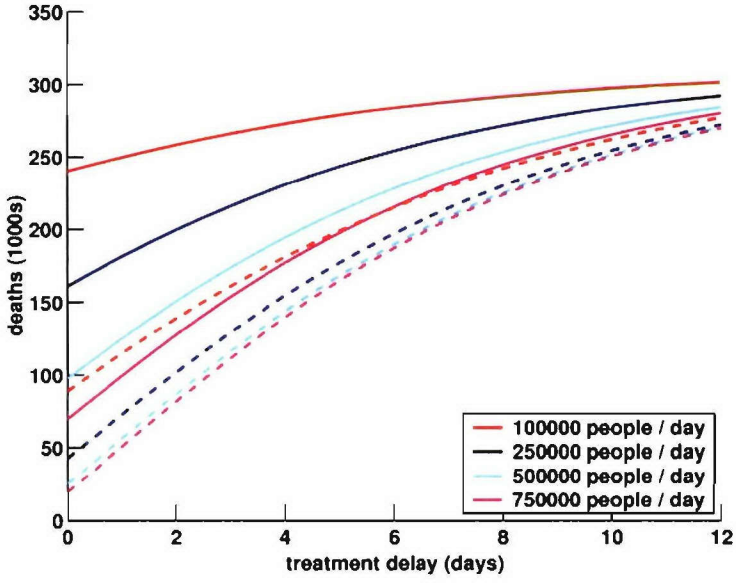

Figure 15. The number of deaths as a function of delay in initiating a public health response, assuming a prophylaxis efficacy of 95%. The curves are colored-coded according to prophylaxis distribution rate as in Figure 12.

5. CONCLUSIONS

The disease progression models can shed light on critical windows of opportunity for public health interventions by quantifying the benefit of early response and high treatment rates. In particular, if antibiotic prophylaxis is distributed at a high rate within the first day following a large anthrax attack, nearly all those exposed can be saved if plume localization is successful. The results indicate plume localization is most beneficial when response is initiated within 2 days post-attack.

Similarly, the smallpox model indicates that early initiation of a mass vaccination campaign and quarantine can significantly reduce the number of deaths. However, the current smallpox model may underestimate the effectiveness of contact tracing for certain outbreaks since it does not model social networks. On the other hand, it is easy to imagine a threshold number of index cases that would overwhelm the contact tracing strategy [28], in which case mass vaccination would likely be the best containment strategy.

6. FUTURE WORK

To more accurately quantify the benefit of early prophylaxis, the differential equation-based model should be updated to a more general transition-based model. The exponential distribution underlies the transitions of the ODE-based model and, as a result, leads to premature transitions between states, in particular the transition from exposed to symptomatic. For example, there were no cases of anthrax 2 days prior to the estimated release date in Sverdlovsk [26]. Thus the ODE model underestimates the benefit of early intervention since treatment is less effective once the individual becomes symptomatic. An updated model will have the option to use probability distribution functions defined by data from outbreaks whenever possible, such as the Sverdlovsk anthrax outbreak [26].

APPENDIX A
MODELING THE NON-INFECTIOUS RECOVERY PERIOD

Given the current assumption that all symptomatic people will be isolated within θ_s^{-1} days, we could use the following equations to estimate the number of physically recovered individuals, $R(t)$.

$$f(S,R) = \rho S \quad \text{(A-1)}$$
$$f(Sq,R) = (\rho + \rho_n)Sq \quad \text{(A-2)}$$
$$f(Sqt,R) = (\rho_t + \rho_{tn})Sqt \quad \text{(A-3)}$$

In this case, nearly all those who become sick move into $R(t)$ from $Sq(t)$ and $Sqt(t)$ with average delays of $\rho^{-1} + \rho_n^{-1}$ and $\rho_t^{-1} + \rho_{nt}^{-1}$ days, respectively. With no capacity limits imposed on isolation, only a fraction of symptomatic people would move to $R(t)$ with a delay of ρ^{-1} days, which would essentially represent a shortened recovery time. However, if the isolation is not assumed, then additional states and equations would be warranted. In particular, a state to hold non-infectious recovering people who are never isolated would be required.

In the case of limited isolation capacity for symptomatic people, one approach to model the number of fully recovered individuals requires one additional state and two additional parameters (a state to hold those individuals who are still recovering but not infectious and two parameters equal to the non-infectious recovery period with and without treatment). We only need one additional state for two reasons. First, we can assume that those in isolation do not spread disease (given the current definition of $\tilde{I}$), so the average transition time between Sq and R can be increased to the infectious period plus the non-infectious recovery period, and similarly for Sqt to R, without increasing disease spread. Second, in the case of a fatal illness, there is no symptomatic yet non-infectious period. In this case, the equations would be

$$f(S,Sn) = \rho S \quad \text{(A-4)}$$
$$f(Sn,R) = \rho_n Sn \quad \text{(A-5)}$$
$$f(Sq,R) = (\rho + \rho_n)Sq \quad \text{(A-6)}$$
$$f(Sqt,R) = (\rho_t + \rho_{tn})Sqt, \quad \text{(A-7)}$$

where Sn is the number of recovery people who are no longer infectious, ρ_n is the non-infectious recovery period, and ρ_{nt} is the non-infectious recovery period with treatment, which would hopefully be the shorter of the two periods.

APPENDIX B
IMPLEMENTATION OF RESOURCE LIMITS

The ODEs presented in the earlier sections were solved using Euler's method with a time step $\Delta t = 0.1$ day prior to the initiation of an epidemic control policy. After the initiation of this policy, the time step is allowed to vary so that the capacities for quarantine and treatment are not exceeded. To do so, we define

$$\Delta t_i = \min(\Delta t, \Delta t_{M_v}, \Delta t_{M_q}, \Delta t_{M_t}, \Delta t_{M_{v_{total}}}, \Delta t_{M_{q_{total}}}), \tag{B-1}$$

where

$$\begin{aligned}
\Delta t_{M_v} &= (M_v - V_{daily}(t_i))/(\Delta V) && \text{(B-2)}\\
\Delta t_{M_q} &= (M_q - Q_{daily}(t_i))/(\Delta Q) && \text{(B-3)}\\
\Delta t_{M_t} &= (M_t - T_{daily}(t_i))/(\Delta T) && \text{(B-4)}\\
\Delta t_{M_{v_{total}}} &= (M_{v_{total}} - V_{total}(t_i))/(\Delta V) && \text{(B-5)}\\
\Delta t_{M_{q_{total}}} &= (M_{q_{total}} - Q_{total}(t_i))/(\Delta Q), && \text{(B-6)}
\end{aligned}$$

where ΔV, ΔQ and ΔT are the number of new people who would be vaccinated, moved into quarantine and treated (determined by evaluating all of the relevant differential equations and assuming a time step of $\Delta t = 0.1$); V_{daily} is a running total of all prophylaxis distributed during the current day; Q_{daily} and T_{daily} are running totals of people in quarantine and treatment respectively; and V_{total} is the number of units of prophylaxis given out so far. Note care must be taken, when the denominator becomes close to zero; this can be addressed by adding a tiny number to the denominator.

At the start of a new 24-hour period, V_{daily} is reset to zero. However, Q_{daily} and T_{daily} are treated differently; people must recover from these states for room to become available.

If the capacity limits for any of the interventions is not met, that is,

$$\begin{aligned}
V_{daily}(t_i) &< M_v && \text{(B-7)}\\
Q_{daily}(t_i) &< M_q && \text{(B-8)}\\
T_{daily}(t_i) &< M_t && \text{(B-9)}\\
V_{total}(t_i) &< M_{v_{total}} && \text{(B-10)}\\
Q_{total}(t_i) &< M_{q_{total}}, && \text{(B-11)}
\end{aligned}$$

then ΔV, ΔQ and ΔT are calculated as follows:

$$\Delta V = \sum_j f(:, j) - \sum_{j \neq Uv} f(Uv, j) - \sum_{j \neq Uqv} f(Uqv, j) - \cdots - \sum_{j \neq Ecv} f(Ecv, j), \tag{B-12}$$

where $j = [Uv\ Uqv\ Ucv\ Ev\ Eqv\ Ecv\ V]$ is a vector of states where people are vaccinated upon entrance. Thus, people moving from Uv into Ev and Uqv into Eqv, etc., are not counted as using

another prophylaxis unit. (For the inhalation anthrax model, $j = [Uv\ Ev\ V]$.) Similarly,

$$\Delta Q = \sum_{j} f(:, j) - \sum_{j \neq Uq} f(Uq, j) - \sum_{j \neq Uqv} f(Uqv, j), \tag{B-13}$$

where $j = [Uq\ Uqv\ Eq\ Eqv\ ]$ is a vector of the non-symptomatic, quarantine states; thus, people moving from Uq into Eq and Uqv into Eqv are not recounted as entering quarantine. Also, note that quarantine capacity does not apply to those who are already symptomatic. (For the inhalation anthrax model, quarantines are not modeled.) And finally,

$$\Delta T = \sum_{j} f(:, j) - \sum_{j \neq St} f(St, j) - \cdots - \sum_{j \neq Sqtd} f(Sqtd, j), \tag{B-14}$$

where $j = [St\ Std\ Sqt\ Sqtd\ ]$ is a vector of states where people undergo treatment upon entering these states; thus, for example, people moving from St into Sqt and Std into $Sqtd$ are not recounted as entering treatment.

APPENDIX C
RESPONSE PARAMETER VALUES

In the next two paragraphs, we describe the parameter values required to initiate the public health responses we are considering (using the Matlab model): (1) contact tracing followed by quarantine and vaccination, (2) mass vaccination, and (3) both of these responses in combination. To simulate contact tracing followed by quarantine and vaccination of contacts but no mass vaccination, set $\theta_c \in (0, 1]$ equal to the proportion of contacts expected to be found, set $M_{q_{total}} \geq M_q > 0$, and set $M_{v_{total}} \geq M_v > 0$. To turn off mass vaccination, set $\nu = 0$. If $\nu = 0$ and $M_{v_{total}} \geq M_v > 0$, then only those contacted will be vaccinated; note, ν or the mass vaccination rate applies only to U and E.

To simulate mass vaccination (of people in U and E) only, define the vaccination rate ($\nu > 0$) and set $M_{v_{total}} \geq M_v > 0$. (If $M_{v_{total}} = M_v = 0$, no one will receive prophylaxis even if $\nu > 0$.) In addition, set $\theta_c = 0$ (so that people in U are not moved to Uc, a state to which mass vaccination does not apply and similarly for E and Ec). If $\theta_c = 0$, then $Uc(t) = 0$ and $Ec(t) = 0$ for all t (and thus, $Ucv(t) = 0$ and $Ecv(t) = 0$ for all t); this ensures that all those unexposed and not vaccinated will remain in U and will receive prophylaxis according to ν and similarly for those in E.

APPENDIX D
ALTERNATE ANTHRAX MODEL

In section 4, we introduced an inhalation anthrax model that assumes that the treatment for prodromal patients is the same unit of prophylaxis distributed during the mass prophylaxis campaign. In this model, people enter the prodromal treatment states ($S1tr$ and $S1t2$) at a rate of ν. We could assume a different treatment scheme for prodromal patients, either the number of people allowed to enter the state can be rate-limited using a different rate, or the number of people allowed to enter can be based on a capacity limit in terms of people. In the first case, the capacity is defined by the number of people treated per day and should be reset daily. In the second case, space in the state becomes available as people recover.

The alternate model described in this section assumes that prophylaxis and the prodromal treatment are different, so states $S1vr$ and $S1v2$ are not needed to ensure that people will not receive prophylaxis twice. In addition, $\tilde{V} = U + E$. Figure D-1 shows a schematic of this model. As a result, ν is replaced by M_{t_1}, and we must redefine the equations governing movement into the treatment states $S1tr$ and $S1t2$, as shown below.

$$f(S1r, S1tr) = \theta_s S1r \quad \text{(D-1)}$$

$$f(S1, S1tr) = (1 - \tilde{\lambda_1})\theta_s S1 \quad \text{(D-2)}$$

$$f(S1, S1t2) = \tilde{\lambda_1}\theta_s S1 \quad \text{(D-3)}$$

Movement into $S1tr$ and $S1t2$ should now be dictated by the capacity limit M_{t_1}, and capacity will not be exceeded by appropriately defining Δt_i as

$$\min(\Delta t, \Delta t_{M_v}, \Delta t_{M_t}, \Delta t_{M_{v_{total}}}), \quad \text{(D-4)}$$

where $\Delta t_{M_t} = \min(\Delta t_{M_{t_1}}, \Delta t_{M_{t_2}}, \Delta t_{M_{t_3}})$ and $\Delta t_{M_{t_1}}, \Delta t_{M_{t_2}}$, and $\Delta t_{M_{t_3}}$ are defined taking into consideration the respective capacity limits:

$$\Delta t_{M_{t_1}} = (M_{t_1} - T_{daily_1}(t_i))/(\Delta T_1) \quad \text{(D-5)}$$

$$\Delta t_{M_{t_2}} = (M_{t_2} - T_{daily_2}(t_i))/(\Delta T_2) \quad \text{(D-6)}$$

$$\Delta t_{M_{t_3}} = (M_{t_3} - T_{daily_3}(t_i))/(\Delta T_3) \quad \text{(D-7)}$$

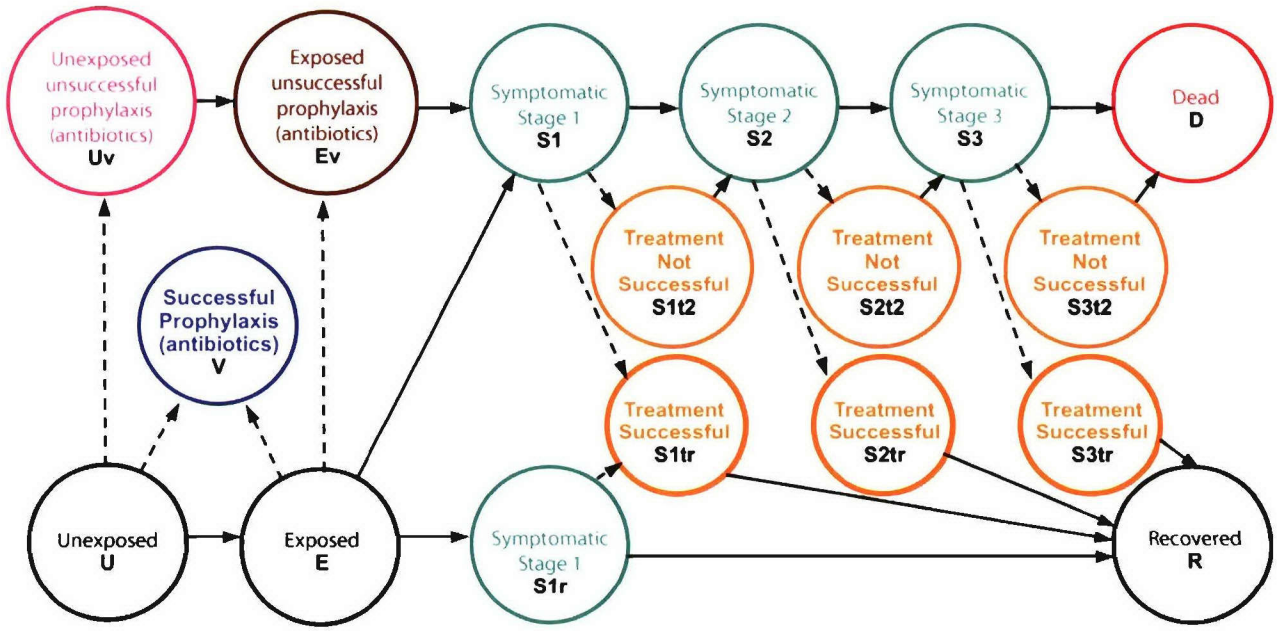

Figure D-1. A schematic showing the allowed movement between states of the alternate anthrax model. The dashed arrows indicate that movement will only occur if related resource limits have not been exceeded.

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